BMJ Open

Registry randomised trials: a methodologic perspective

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068057
Article Type:	Communication
Date Submitted by the Author:	12-Sep-2022
Complete List of Authors:	Doherty, Dorota; The University of Western Australia; King Edward Memorial Hospital for Women Perth, Biostatistics and Research Design Unit Tong, Steven; The Peter Doherty Institute for Infection and Immunity; Menzies School of Health Research Reilly, Jennifer; Alfred Hospital, Anaesthesiology & Perioperative Medicine; Monash University, Department of Anaesthesia and Perioperative Medicine Shrapnel, Jane; The Sydney Children's Hospitals Network McDonald , Stephen ; The University of Adelaide, Central Northern Adelaide Dialysis; South Australian Health and Medical Research Institute Limited, Australia and New Zealand Dialysis and Transplant Registry Ahern, Susannah; Monash University Department of Epidemiology and Preventive Medicine Harris, Ian; UNSW, Ingham Institute for Applied Medical Research, South Western Sydney Clinical School Tam, Charmaine S.; The University of Sydney, Northern Clinical School, Centre for Translational Data Science Brennan, Angela; Monash University Department of Epidemiology and Preventive Medicine Hodgson, Carol; Monash University Wilcox, Leonie; St Vincent's Health Australia Ltd, Australasian Bone Marrow Transplant Recipient Registry Balagurunathan, Anitha; Alfred Health, Epidemiology Butcher, Belinda; WriteSource Medical Pty Ltd; University of New South Wales Faculty of Medicine, Reid, Christopher; Monash University, School of Public Health and Preventive Medicine; Curtin University, School of Public Health
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Communication
Keywords:	STATISTICS & RESEARCH METHODS, PUBLIC HEALTH, BIOTECHNOLOGY & BIOINFORMATICS

Communication

Registry randomised trials: a methodologic perspective

Dorota A Doherty[1,2], Steven Tong[3,4], Jennifer R Reilly[5,6], Jane Shrapnel[7], Stephen P. McDonald[8,9], Susannah Ahern[10], Ian A Harris[11], Charmaine Tam[12], Angela Brennan[10], Carol Hodgson[13,14,15], Leonie Wilcox[16], Anitha Balagurunathan[17], Belinda E Butcher[18,19], Christopher M Reid[11,12,20]

Corresponding Author:

Christopher Reid
School of Population Health
Curtin University, WA
T: +61 8 9266 7123

[1] Biostatistics and Research Design Unit, Women and Infants Research Foundation, King Edward Memorial Hospital for Women, Subiaco WA
[2] Division of Obstetrics and Gynaecology, University of Western Australia, Subiaco, WA
[3] Victorian Infectious Diseases Service, The Royal Melbourne Hospital, at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
[4] Department of Infectious Diseases, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
[5] Department of Anaesthesiology and Perioperative Medicine, Alfred Hospital, Melbourne, VIC
[6] Department of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, VIC
[7] Sydney Children's Hospital Network, Westmead, NSW
[8] Adelaide Medical School, University of Adelaide, Adelaide, SA
[9] Australia and New Zealand Dialysis and Transplant Registry, South Australia Health and Medical Research Institute
[10] Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC
[11] Ingham Institute for Applied Medical Research, South Western Sydney Clinical School, University of New South Wales, Sydney, NSW
[12] Northern Clinical School, Centre for Translational Data Science, The University of Sydney, NSW
[13] Division of Clinical Trials and Cohort Studies, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC
[14] Australian and New Zealand Intensive Care-Research Centre, Monash University, Melbourne, VIC
[15] The Alfred Hospital, Melbourne, VIC
[16] Australasian Bone Marrow Transplant Recipient Registry, The Kinghorn Cancer Centre, Darlinghurst NSW
[17] Australian Clinical Trials Alliance, South Melbourne, VIC
[18] WriteSource Medical Pty Ltd, Lane Cove, NSW
[19] School of Medical Sciences UNSW, UNSW Sydney, NSW
[20] School of Population Health, Curtin University, WA

E: christopher.reid@curtin.edu.au

Abstract

Registry randomised clinical trials (RRCTs) have the potential to provide pragmatic answers to important clinical questions. RRCTs can be embedded into large population-based registries or smaller single site registries to provide timely answers at a reduced cost compared to traditional randomised controlled trials. RRCTs can take a number of forms in addition to the traditional individual-level randomised trial, including parallel group trials, platform or adaptive trials, cluster randomised trials (CRT), and cluster randomised stepped-wedge trials (SW-CRT). From an implementation perspective, initially it is advantageous to embed RRCT into well-established registries as these have typically already overcome any issues with endpoint validation and adjudication. With advances in data linkage and data quality, RRCTs can play an important role in answering clinical questions in a pragmatic, cost-effective way.

Introduction

In Australia, clinical quality registries are encouraged by the Australian Commission on Safety and Quality in Health Care to identify benchmarks and variation in clinical outcomes, feeding back information to health care providers, patients, and government to inform clinical practice.[1] Clinical quality registries have matured over the past two decades and guidance for their establishment in Australia now aligns with the *Framework for Australian Clinical Quality Registries (2014).*[1] In early 2021, the Australian Government released a national strategy for clinical quality registries and virtual registries.[2] Outside of the quality framework, clinical registries may also be set up to collect safety data, disease or procedure information, and to measure translation of evidence-based medicine into practice.

This review considers the benefits of RRCT, the types of questions they can answer, and some practical tips on how to successfully embed registry randomised trials. It is based on a series of workshops held by the Australian Clinical Trials Alliance (ACTA) in May 2020. A glossary of terms used throughout is provided as Table 1.

Registries may have a large and broad target population, established to monitor high level activity and outcomes on a population basis; or may have a much smaller reach (e.g., a single hospital, or several hospitals within a single state, or a niche area of investigation such as a disease, a treatment, or a device), but with much deeper data capture. Clinical registries allow collection of 'real-world' data in from patients in a clinical setting, many of whom would be excluded from randomised clinical trials.[3] There are six pillars underpinning clinical quality registries (see Table 2).

Clinical registries positively impact the quality of patient healthcare and health outcomes.[4 5] An Australian evaluation reported that registries improve the value of healthcare delivery at a relatively low cost, therefore producing high returns on investment.[6] While registries are often designed for such quality and safety purposes, they can also provide a platform to answer pragmatic questions. Registry randomised controlled trials (RRCTs) can be embedded into

both large population-based registries (e.g. health services registries) and smaller registries (e.g. disease or procedure registries).

RRCTs complement more traditional randomised controlled trials. While randomised controlled trials remain the gold standard for demonstrating efficacy, they are limited by the time they take, their costs and their limited external validity.[7] One of the main problems with conventional RCTs is often restrictive eligibility criteria, which limits the generalisability between clinical trial populations and the target population.[8] Although RRCTs can reduce the problem of generalisability, the extent to which this occurs is dependent both upon characteristics of the registry and design of the embedded clinical trial.[8] The advantages and disadvantages of RRCT are listed in Table 3.

By using existing infrastructure, RRCTs may: deliver answers to key clinical questions efficiently and at a lesser cost; have the potential to engage a broad range of stakeholders; have an inbuilt ability to collect long-term follow-up data; and can improve generalisability of results.[7 9] Further, given the cost of running a RRCT is significantly less than the traditional RCT model, RRCTs may have a key role in evaluating important clinical questions where funding is difficult to access, for example, evaluation of generic pharmacotherapies,[10] medical devices and clinical procedures.[9]

Endpoint validation is an important consideration, particularly where data are collected from different institutions: there must be consistency in data definition and data collection. A fundamental difference from clinical trials endpoints, which are chosen or designed to meet the needs of the intervention, registry-based endpoints may have been designed for vastly different purposes. The accuracy of clinical endpoint determination using registry data as compared to active source data collection, follow-up, and clinical adjudication is currently unknown. Some registry outcomes may be linked or aligned to ICD-10 codes. Internationally, Australia is unique in its adoption of ICD-10 coding for hospital reimbursement, and coding standards differ between states and territories. There is some evidence to suggest poor

agreement between ICD-10 coding and clinical audit.[11] Adjudication of events within registry trials may therefore be necessary to ensure the quality of risk factor and outcomes data.[7] One approach is having a *Clinical Event Adjudication Committee* adjudicate a subset of randomly identified events. Linking data to other datasets (e.g. National Death Index) can also be used for validation, where such datasets are available.

What designs are available for RRCT?

RRCTs are particularly useful when assessing real-world implementation of interventions.[7] RRCTs can take a number of designs, including individual level randomised controlled trials, parallel group trials, platform or adaptive trials, cluster randomised trials (CRT), and stepped-wedge cluster randomised trials (SW-CRT). Adaptive randomisation may occur within pre-specified subgroups. While randomisation at the individual level has been more commonly used in RRCTs to date,[7] cluster randomisation is increasingly reported,[7 12] and has several distinct advantages, including overcoming administrative barriers and reducing costs.[12]

Several types of *cluster randomised trial* design may be used in RRCTs (see Figure 1). In each of these study types, clusters (e.g., hospitals, GP practices etc) are randomised rather than individual patients. Similar to other trial designs, in cluster randomised trials the clustering effects need to be considered. For example, we might expect that mortality risk would vary across intensive care units, but patients within the same intensive care unit are likely to have similar mortality risk. This is called 'within-cluster correlation', and as such, the information per patient is not independent. There is some loss of statistical information in cluster randomised trials which leads to increased sample sizes requirements, however, this is typically offset by the ease of identifying and recruiting patients.

Parallel cluster RCT are similar to individual patient RCTs, except that randomisation occurs at the level of the cluster rather than the patient. Each cluster is randomly allocated to an intervention and remains with that intervention for the duration of the trial. In these studies, the information per patient is not independent leading to a loss of information,

counterbalanced by greater number of recruited patients. However, these studies are relatively simple to analyse and interpret.

In the *cluster crossover* design, clusters switch between interventions, and the effect of the intervention is estimated by comparisons within each cluster, removing the between-cluster variability. Thus, this design requires fewer clusters and fewer patients than the parallel design. However, in this design, within-period correlations and between-period correlations must both be considered, and the design necessitates that the between-period correlation is smaller than the within-period correlation, because their relative size determines the value of the crossover. Not all individually randomised trials are suitable for conduct as a cluster crossover trial: treatments must be able to be implemented and withdrawn easily; carryover effects must be avoided; and all patients must be recruited from the registry.

Stepped-wedge cluster randomised trial designs are beneficial where there is a risk of individuals in the control arm being accidentally exposed to the intervention. They are particularly useful in the general practice setting, or when implementing guidelines, training or system changes. In a SW-CRT design, all clusters start in the control phase and randomisation determines the order in which the intervention is implemented. Clusters (or groups of clusters) are randomly assigned to a time point when they cross over from control to intervention phase (step/sequence/arm). The SW-CRT can be designed with data collected cross-sectionally from different samples of individuals at each timepoint. Alternatively, data may be collected from a closed cohort, where individuals are followed longitudinally over the entire period of the trial and repeated measures are taken on the same individual at each time point. No new individuals join after the study starts. In an open cohort, data are collected on the same individuals over time, but new individuals can join over the study duration. At the end of the trial all clusters are in the intervention phase. Clusters are followed-up longitudinally, with outcomes/endpoints usually measured at discrete time points on individuals.

In SW-CRT, the sample size calculations need to allow for the effects of randomising clusters instead of individuals, those attending the same institution are more likely to have similar results than those attending elsewhere. The positive correlation of individuals within the same cluster is quantified with the intra-cluster correlation (ICC). The ICC measures the proportion of the total variance attributable to the variance between clusters. The extra variability between clusters in CRT has implications for the sample size and analysis. SW-CRT assume the full effect of the intervention occurs at the same time interval when intervention is introduced. A delay of intervention effect reduces the study power given a fixed number of cluster and participants. One approach to ensure that the required power is maintained is to add additional measurement periods.

Advantages and disadvantages of various RRCT designs are summarised in Table 4.

Extracting data from the electronic medical record to develop virtual registries

Electronic data capture and integration with the electronic medical record has the potential to improve data validity and the efficiency of data collection, both of critical importance for clinical trials.[5] Utilising routinely collected medical record data in an automated fashion for determining clinical trial eligibility according to inclusion and exclusion criteria could greatly facilitate trial recruitment. Using routinely collected electronic medical record data, entered by clinicians at the time of diagnosis and treatment, for automated outcome ascertainment may also reduce time and costs and efficiency in conducting trials. There has been interest in using medical records as a data source for performing clinical analytics as early as the 1960s.[13] Medical records contain a tremendous accumulation of data, and it was hoped that electronic data processing systems would allow for organised, chronological records of patient information that could be used to facilitate research and hospital reporting.[13] It has recently been suggested that linkage of electronic medical records can be successfully used to

provide near real-time clinical audit with feedback to clinicians, and provide a framework for clinical decision support.[14]

Overcoming the technical and legal issues associated with data linkage to the electronic medical record can be a barrier;[5] not the least that there are a large number of different electronic medical record (eMR) platforms currently in use. The majority of data exist in the electronic medical record as free text, requiring careful mapping and validation. Text mining and natural language processing approaches to electronic medical records may assist in accurate patient identification and data collection. This requires a collaborative approach including the eMR developer, data architect, data scientist, data analyst and clinician. There are already successful examples of combining data from registries with the electronic health record.[15] The development of privacy preserved record linkage capabilities will further facilitate the extended linking of administrative and clinical trial datasets for monitoring of health outcomes.[16] This approach to data linkage has been highlighted as a priority area for clinical quality registries in order to facilitate their use for research purposes.[2]

Embedding trials into registries

In order to embed trials into registries, triallists must reach a compromise between a 'broad but shallow' data collection methodology typical of many registries, and the 'narrow but deep' approach for trial-related data collection, often needing to accept simpler accountability than seen in more traditional RCT approaches. In countries with well-established national registries, with standardised endpoints and little missing data, RRCTs offer a viable alternative to RCTs for generating high-quality clinical evidence.[7] By addressing issues of endpoint validity and adjudication, and decreasing the proportion of missing data, smaller disease or procedure focused registries might be able to improve the quality of their evidence, and in turn become a viable alternative platform than more costly RCTs.[7] For this reason it may be advantageous to initially embed RRCTs into registries that are already well established [7]. Internationally, registry data are becoming increasingly important in regulatory

assessments, especially for post-marketing safety and effectiveness studies.[17] The key pillars when considering embedding a RRCT are outlined in Figure 2.

Best practice requires registries to be adequately resourced, so that data quality is maximised. Should the RRCT be a feasible option for a given registry and for a clinical questions, careful delineation of responsibilities regarding randomisation, missing data, handling of data queries, data quality, data extraction, and management of serious adverse event information need to be considered. We suggest that the first two are the responsibility of the registry, the last is the responsibility of the trialist, and data queries could be attended to by either the registry or triallist. This requires adequate funding both of the registry itself and the RCT embedded within it. However, the benefits may far outweigh the cost. RRCTs allow for potential collaboration between clinical trial networks and clinical quality registries in related disciplines. The shared data management responsibilities between these potentially avoids data wastage for once-only use in more traditional clinical trials, and also improves the quality of data available within the registry. In some cases RRCTs may not the best approach, such as in earlier phase 2 or phase 3 clinical trials.

One of the key benefits of embedding clinical trials into registries is that following the trial's conclusion, the translation of evidence generated within that trial can then be assessed using the ongoing clinical registry. This addresses one of the key drawbacks of traditional randomised trials – there is no direct way to measure whether or not their findings have been implemented, and whether they translate to real-world practice.

Finally, there is also increasing interest in facilitating long-term follow-up post RCT using linked administrative and registry data.[18]

Conclusion

Registries offer a unique platform within which to conduct RCTs. With appropriate registry selection and clinical trial design, and advances in data linkage and data quality, RRCTs can play an important role in answering clinical questions in a pragmatic, cost-effective way.

Authors contributions

As per ICMJE criteria for authorship, all authors (DAD, ST, JRR, JS, SPM, SA, IAH, CT, AB, CH, LW, AB, BEB and CMR) made substantial contributions to the conception of this work, drafting the manuscript or revising it critically for important intellectual content, and approved the final version to be published. All authors (DAD, ST, JRR, JS, SPM, SA, IAH, CT, AB, CH, LW, AB, BEB and CMR) agree to be accountable for all aspects of the work in ensuring that questions raised relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding statement

This work was supported by an Australian Government Medical Research Future Fund grant thought the 2017 Lifting Clinical Trials and Registries Capacity - Clinical Trials Networks Program.

Competing Interest

CMR is funded through a NHMRC Principal Research Fellowship (GHT1136372). CH is funded by a national Heart Foundation Fellowship and an NHMRC Investigator Grant. JR is funded by an Australian Government Research Training Program (RTP) Scholarship and a Monash University Graduate Excellence Scholarship.

References

1. Australian Commission on Safety and Quality in Health Care. National arrangements for clinical quality registries. Available from https://www.safetyandquality.gov.au/our-work/indicators-measurement-and-reporting/national-arrangements-clinical-quality-registries Accessed 2 December 2020. 2019 [

2. Australian Government - Department of Health. National Clinical Quality Registry and Virtual Registry Strategy 2020-2030, 2021.

3. Gitt AK, Bueno H, Danchin N, et al. The role of cardiac registries in evidence-based medicine. *Eur Heart J* 2010;31(5):525-9. doi: 10.1093/eurheartj/ehp596 [published Online First: 2010/01/23]

4. Hoque DME, Kumari V, Hoque M, et al. Impact of clinical registries on quality of patient care and clinical outcomes: A systematic review. *PLoS One* 2017;12(9):e0183667. doi: 10.1371/journal.pone.0183667 [published Online First: 2017/09/09]

5. Sparring V, Granström E, Andreen Sachs M, et al. One size fits none – a qualitative study investigating nine national quality registries' conditions for use in quality improvement, research and interaction with patients. *BMC Health Services Research* 2018;18(1) doi: 10.1186/s12913-018-3621-9

6. Australian Commission on Safety and Quality in Health Care. Economic evaluation of clinical quality registries: Final report. Sydney: ACSQHC, 2016.

7. Karanatsios B, Prang KH, Verbunt E, et al. Defining key design elements of registry-based randomised controlled trials: a scoping review. *Trials* 2020;21(1):552. doi: 10.1186/s13063-020-04459-z [published Online First: 2020/06/24]

8. Lasch F, Weber K, Koch A. Commentary: On the levels of patient selection in registry-based randomized controlled trials. *Trials* 2019;20(1):100. doi: 10.1186/s13063-019-3214-x [published Online First: 2019/02/06]

9. James S, Rao SV, Granger CB. Registry-based randomized clinical trials--a new clinical trial paradigm. *Nat Rev Cardiol* 2015;12(5):312-6. doi: 10.1038/nrcardio.2015.33 [published Online First: 2015/03/18]

10. Yndigegn T, Hofmann R, Jernberg T, et al. Registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era. *Heart* 2018;104(19):1562-67. doi: 10.1136/heartjnl-2017-312322 [published Online First: 2018/04/19]

11. Reilly JR, Shulman MA, Gilbert AM, et al. Towards a national perioperative clinical quality registry: the diagnostic accuracy of administrative data in identifying major postoperative complications. *Anaesth Intensive Care* 2020:310057X20905606. doi: 10.1177/0310057X20905606 [published Online First: 2020/04/30]

12. Moberg J, Kramer M. A brief history of the cluster randomised trial design. *Journal of the Royal Society of Medicine* 2015;108(5):192-8. doi: 10.1177/0141076815582303 [published Online First: 2015/05/30]

13. Baird HW, Garfunkel JM. Electronic Data Processing of Medical Records. *New England Journal of Medicine* 1965;272(23):1211-15. doi: 10.1056/nejm196506102722306

14. Saavedra A, Morris RW, Tam CS, et al. Validation of acute myocardial infarction (AMI) in electronic medical records: the SPEED-EXTRACT study. 2020 doi: 10.1101/2020.12.08.20245720

15. Kibbelaar RE, Oortgiesen BE, van der Wal-Oost AM, et al. Bridging the gap between the randomised clinical trial world and the real world by combination of population-based registry and electronic health record data: A case study in haemato-oncology. *Eur J Cancer* 2017;86:178-85. doi: 10.1016/j.ejca.2017.09.007 [published Online First: 2017/10/11]

16. Brown AP, Randall SM, Ferrante AM, et al. Estimating parameters for probabilistic linkage of privacy-preserved datasets. *BMC Med Res Methodol* 2017;17(1):95. doi: 10.1186/s12874-017-0370-0 [published Online First: 2017/07/12]

17. McGettigan P, Alonso Olmo C, Plueschke K, et al. Patient Registries: An Underused Resource for Medicines Evaluation. *Drug Safety* 2019;42(11):1343-51. doi: 10.1007/s40264-019-00848-9

18. Fitzpatrick T, Perrier L, Tricco AC, et al. Protocol for a scoping review of post-trial extensions of randomised controlled trials using individually linked administrative and registry data. *BMJ open* 2017;7(2):e013770. doi: 10.1136/bmjopen-2016-013770 [published Online First: 2017/02/19]

19. Li G, Sajobi TT, Menon BK, et al. Registry-based randomized controlled trials- what are the advantages, challenges, and areas for future research? *J Clin Epidemiol* 2016;80:16-24. doi: 10.1016/j.jclinepi.2016.08.003 [published Online First: 2016/10/22]

20. Donner A, Klar N. Pitfalls of and controversies in cluster randomization trials. *Am J Public Health* 2004;94(3):416-22. doi: 10.2105/ajph.94.3.416 [published Online First: 2004/03/05]

21. Peptic Investigators for the Australian New Zealand Intensive Care Society Clinical Trials Group AHSCCSCN, The Irish Critical Care Trials Group, Young PJ, et al. Effect of Stress Ulcer Prophylaxis With Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation: The PEPTIC Randomized Clinical Trial. *Jama* 2020;323(7):616-26. doi: 10.1001/jama.2019.22190 [published Online First: 2020/01/18]

22. Li AH, Garg AX, Prakash V, et al. Promoting deceased organ and tissue donation registration in family physician waiting rooms (RegisterNow-1 trial): study protocol for a pragmatic, stepped-wedge, cluster randomized controlled registry. *Trials* 2017;18(1):610. doi: 10.1186/s13063-017-2333-5 [published Online First: 2017/12/23]

Tables

Table 1: Glossary of Terms

Term	Definition
Clinical quality registry	Clinical quality registries use clinical data to identify benchmarks and variation in clinical outcomes and feed-back essential risk-adjusted clinical information, to clinicians, patients, consumers, health service administrators and government to inform clinical practice and health service decision making [1].
Cluster	A cluster is a group of patients. It may be a hospital, a GP practice, a group of patients treated by an individual clinician etc.
Cluster crossover trial	A cross-over trial where the unit of randomisation is a cluster.
Cluster randomised trial	A randomised trial where the unit of randomisation is a cluster.
Cross over trial (individual patient randomisation)	A cross-over trial where the unit of randomisation is the patient. A crossover trial involves patients being treated sequentially with two (or more) treatments of interest.
Parallel arm trial (individual patient randomisation)	A trial where the unit of randomisation is the patient. Patients are randomised to receive one treatment of interest.

Parallel cluster randomised controlled trial	A trial where clusters are randomised to receive one treatment of interest.
Registry randomised clinical trial	A randomised clinical trial that is embedded into a registry.
Stepped-wedge cluster randomised trial	A trial where clusters are randomised to receive control then intervention/treatment in a stepped fashion. That is, the timing of the switch to intervention/treatment is randomised (see also Figure 1).

Table 2: Six pillars underpinning clinical quality registries in Australia

1. Patient-centred health care

   Registries can help to identify variability in patient reported outcomes; support clinicians to tailor care to individual needs and preferences; support equity of health care. Datasets should therefore contain a combination of clinician and patient-derived data; and should have clinician oversight.

2. Improved clinical practice care and patient outcomes

   Datasets should have mechanisms for 'benchmarking' where clinicians, health service and other stakeholders are provided with feedback on their care provision 'benchmarking'.

3. Quality, efficiency and cost effectiveness

   Improve the quality and efficiency of data collection. Improve governance and allow data sharing: 'collect one, use multiple times principle'. This requires data linkage, where possible, to reduce burden. Data collection should be standardised, and follow national health data and terminology standards and definitions.

4. Financial sustainability

   Sufficient, sustainable funding is required. The funding model may include partnerships with multiple beneficiaries. In this context, funding via clinical trials might also be appropriate.

5. Transparency and access

   Timely provision of tailored information to patients, hospitals, jurisdictions,

governments, funders, private health insurers, researchers and other stakeholders, while upholding patient privacy.

6. Data linkage, integration and interoperability

By improving linkage, a more comprehensive, longitudinal picture of patient treatment and outcomes than is currently available will be possible. This will also allow for increased analytical power and provide more cost effective clinical trials and more comprehensive post-market surveillance of devices and medicines.

Table 3: Advantages and disadvantages of RRCT

Potential Advantages	Potential Disadvantages
• In many cases, reduced time for data collection compared to RCT [4] • Reduced database costs compared to RCT as embedded into existing infrastructure • reduced data collection costs as data extracted for the registry is leveraged for the clinical trial • Include patients identified and recruited from within a registry [19] • All interventions and outcomes are captured in the registry [19] • Less selected patient population compared to traditional RCT [9] hence improved external validity compared to traditional RCT [7 8]	• Limited endpoint selection • Endpoints might not be well defined [9] • Missing data • Variable data quality [9] • Data entry may occur sometime after original clinical data collection

Table 4: Advantages and disadvantages of various registry randomised controlled trial designs

Design	Advantages	Disadvantages
Parallel group cluster RCT	• Easy to analyse and interpret • Randomisation removes potential confounding [9] • Increased administrative efficiency [20] • Easy to recruit patients [7] • Cost effective [7] • Potential for large number of events allows for identification of rare events [9]	• Increased risk of bias compared to individual patient RCT • Limited possibility for collection of detailed safety reporting [9] • Less efficient than individual level RCT
Cluster crossover RCT e.g PEPTIC [21] (see Case Study 3)	• Randomisation removes potential confounding [9] • Randomised clusters serve as their own controls • Avoids potential contamination of control with intervention [20] • Includes all patients within a cluster	• Increased risk of bias compared to individual patient RCT • Increased burden on participants • Not all studies can be implemented using these methods: treatments must be able to be implemented and withdrawn easily

	• Assumes consent of patient (or recruitment often occurs under a waiver of consent) • Easy to recruit patients [7] • Cost effective [7] • Potential for large number of events allows for identification of rare events [9]	• Risk of carry over effects • Limited possibility for collection of detailed safety reporting [9] • Take longer to complete than a parallel group cluster RCT • Ethics committees may not be supportive of waiver of consent
Cluster stepped-wedge e.g. RegisterNow-1 [22] (See Case Study 4)	• Randomisation removes potential confounding [9] • Avoids potential contamination of control with intervention [20] • Easy to recruit patients [7] • Cost effective [7] • Potential for large number of events allows for identification of rare events [9]	• Takes longer to complete • Increased burden on participants • Increased risk of bias compared to individual patient RCT • No consensus for best approach to analysis • Limited possibility for collection of detailed safety reporting [9]

Figures

Figure 1: Possible designs for registry randomised trials

Figure 2: Key pillars when considering embedding a RRCT [17]

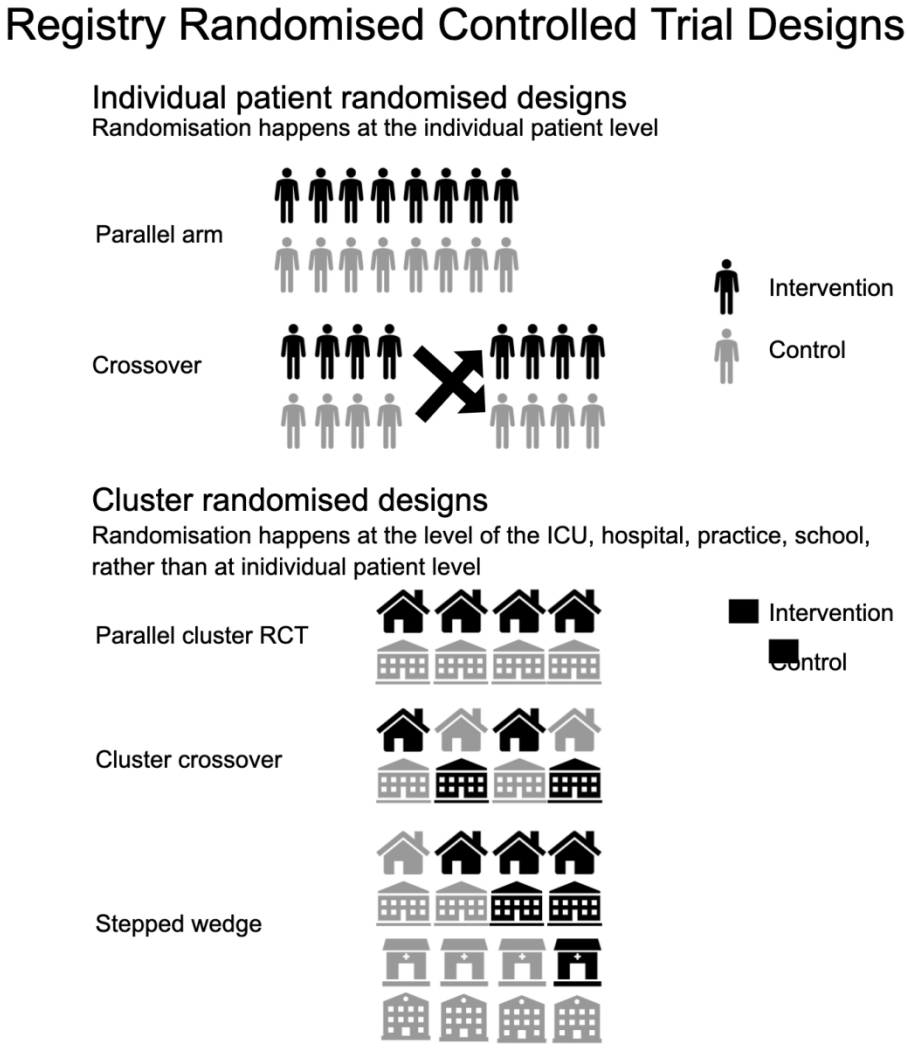

Figure 1: Possible designs for registry randomised trials

127x134mm (300 x 300 DPI)

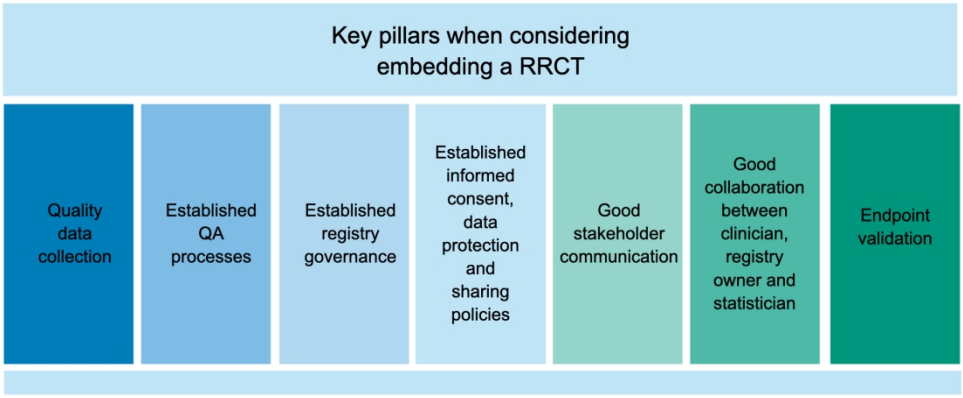

Figure 2: Key pillars when considering embedding a RRCT

172x71mm (300 x 300 DPI)

BMJ Open

Registry randomised trials: a methodologic perspective

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068057.R1
Article Type:	Communication
Date Submitted by the Author:	02-Feb-2023
Complete List of Authors:	Doherty, Dorota; The University of Western Australia; King Edward Memorial Hospital for Women Perth, Biostatistics and Research Design Unit Tong, Steven; The Peter Doherty Institute for Infection and Immunity; Menzies School of Health Research Reilly, Jennifer; Alfred Hospital, Anaesthesiology & Perioperative Medicine; Monash University, Department of Anaesthesia and Perioperative Medicine Shrapnel, Jane; The Sydney Children's Hospitals Network McDonald , Stephen ; The University of Adelaide, Central Northern Adelaide Dialysis; South Australian Health and Medical Research Institute Limited, Australia and New Zealand Dialysis and Transplant Registry Ahern, Susannah; Monash University Department of Epidemiology and Preventive Medicine Harris, Ian; UNSW, Ingham Institute for Applied Medical Research, South Western Sydney Clinical School Tam, Charmaine S.; The University of Sydney, Northern Clinical School, Centre for Translational Data Science Brennan, Angela; Monash University Department of Epidemiology and Preventive Medicine Hodgson, Carol; Monash University Wilcox, Leonie; St Vincent's Health Australia Ltd, Australasian Bone Marrow Transplant Recipient Registry Balagurunathan, Anitha; Alfred Health, Epidemiology Butcher, Belinda; WriteSource Medical Pty Ltd; University of New South Wales Faculty of Medicine, Reid, Christopher; Monash University, School of Public Health and Preventive Medicine; Curtin University, School of Public Health
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Communication
Keywords:	STATISTICS & RESEARCH METHODS, PUBLIC HEALTH, BIOTECHNOLOGY & BIOINFORMATICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in BMJ Open and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Communication

Registry randomised trials: a methodologic perspective

Dorota A Doherty[1,2], Steven Tong[3,4], Jennifer R Reilly[5,6], Jane Shrapnel[7], Stephen P. McDonald[8,9], Susannah Ahern[10], Ian A Harris[11], Charmaine Tam[12], Angela Brennan[10], Carol Hodgson[13,14,15], Leonie Wilcox[16], Anitha Balagurunathan[17], Belinda E Butcher[18,19], Christopher M Reid[11,12,20]

Corresponding Author:

Christopher Reid
School of Population Health
Curtin University, WA
T: +61 8 9266 7123

[1] Biostatistics and Research Design Unit, Women and Infants Research Foundation, King Edward Memorial Hospital for Women, Subiaco WA
[2] Division of Obstetrics and Gynaecology, University of Western Australia, Subiaco, WA
[3] Victorian Infectious Diseases Service, The Royal Melbourne Hospital, at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
[4] Department of Infectious Diseases, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
[5] Department of Anaesthesiology and Perioperative Medicine, Alfred Hospital, Melbourne, VIC
[6] Department of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, VIC
[7] Sydney Children's Hospital Network, Westmead, NSW
[8] Adelaide Medical School, University of Adelaide, Adelaide, SA
[9] Australia and New Zealand Dialysis and Transplant Registry, South Australia Health and Medical Research Institute
[10] Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC
[11] Ingham Institute for Applied Medical Research, South Western Sydney Clinical School, University of New South Wales, Sydney, NSW
[12] Northern Clinical School, Centre for Translational Data Science, The University of Sydney, NSW
[13] Division of Clinical Trials and Cohort Studies, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC
[14] Australian and New Zealand Intensive Care-Research Centre, Monash University, Melbourne, VIC
[15] The Alfred Hospital, Melbourne, VIC
[16] Australasian Bone Marrow Transplant Recipient Registry, The Kinghorn Cancer Centre, Darlinghurst NSW
[17] Australian Clinical Trials Alliance, South Melbourne, VIC
[18] WriteSource Medical Pty Ltd, Lane Cove, NSW
[19] School of Medical Sciences UNSW, UNSW Sydney, NSW
[20] School of Population Health, Curtin University, WA

E: christopher.reid@curtin.edu.au

Abstract

Registry randomised clinical trials (RRCTs) have the potential to provide pragmatic answers to important clinical questions. RRCTs can be embedded into large population-based registries or smaller single site registries to provide timely answers at a reduced cost compared to traditional randomised controlled trials. RRCTs can take a number of forms in addition to the traditional individual-level randomised trial, including parallel group trials, platform or adaptive trials, cluster randomised trials (CRT), and cluster randomised stepped-wedge trials (SW-CRT). From an implementation perspective, initially it is advantageous to embed RRCT into well-established registries as these have typically already overcome any issues with endpoint validation and adjudication. With advances in data linkage and data quality, RRCTs can play an important role in answering clinical questions in a pragmatic, cost-effective way.

Introduction

In Australia, clinical quality registries are encouraged by the Australian Commission on Safety and Quality in Health Care to identify benchmarks and variation in clinical outcomes, feeding back information to health care providers, patients, and government to inform clinical practice [1]. Clinical quality registries have matured over the past two decades and guidance for their establishment in Australia now aligns with the *Framework for Australian Clinical Quality Registries (2014) [1]*. In early 2021, the Australian Government released a national strategy for clinical quality registries and virtual registries [2]. Outside of the quality framework, clinical registries may also be set up to collect safety data, disease or procedure information, and to measure translation of evidence-based medicine into practice.

Unlike Australia, a number of countries have well established clinical registries and, for more than a decade, have developed the capability to undertake embedded randomised trials across a variety of clinical disciplines [3-6]. A well conducted scoping review identified 17 published trials using disease, procedure or health services registries [7]. One of the early demonstrations of the RRCTs was the TASTE Trial undertaken in the SWEDEHEART clinical registry demonstrating no benefit of thrombus aspiration prior to percutaneous coronary intervention for improving clinical outcomes [8]. Heralded as the "next disruptive technology" for undertaking randomised trials [9], the SwedeHeart registry has continued to perform a number of important comparative effectiveness trials and proposing international registry based randomised trials.

This review considers the benefits of RRCT, the types of questions they can answer, and some practical tips on how to successfully embed registry randomised trials into the Australian health care setting. It is based on a series of workshops held by the Australian Clinical Trials Alliance (ACTA) in May 2020. A glossary of terms used throughout is provided as Table 1.

Development of Clinical Quality Registries in Australia

Registries may have a large and broad target population, established to monitor high level activity and outcomes on a population basis; or may have a much smaller reach (e.g., a single hospital, or several hospitals within a single state, or a niche area of investigation such as a disease, a treatment, or a device), but with much deeper data capture. Clinical registries allow collection of 'real-world' data in from patients in a clinical setting, many of whom would be excluded from randomised clinical trials [10]. There are six pillars underpinning clinical quality registries (see Table 2).

Clinical registries positively impact the quality of patient healthcare and health outcomes [11 12]. An Australian evaluation reported that registries improve the value of healthcare delivery at a relatively low cost, therefore producing high returns on investment [13]. While registries are often designed for such quality and safety purposes, they can also provide a platform to answer pragmatic questions. Registry randomised controlled trials (RRCTs) can be embedded into both large population-based registries (e.g. health services registries) and smaller registries (e.g. disease or procedure registries).

RRCT Design Considerations

RRCTs complement more traditional randomised controlled trials. While randomised controlled trials remain the gold standard for demonstrating efficacy, they are limited by the time they take, their costs and their limited external validity [7]. One of the main problems with conventional RCTs is often restrictive eligibility criteria, which limits the generalisability between clinical trial populations and the target population [14]. Although RRCTs can reduce the problem of generalisability, the extent to which this occurs is dependent both upon characteristics of the registry and design of the embedded clinical trial [14]. The advantages and disadvantages of RRCT are listed in Table 3.

By using existing infrastructure, RRCTs may: deliver answers to key clinical questions efficiently and at a lesser cost; have the potential to engage a broad range of stakeholders; have an inbuilt ability to collect long-term follow-up data; and can improve generalisability of results [7 15]. Further, given the cost of running a RRCT is significantly less than the traditional RCT model, RRCTs may have a key role in evaluating important clinical questions where funding is difficult to access, for example, evaluation of generic pharmacotherapies [16], medical devices and clinical procedures [15].

Trial Population Representativeness

An added benefit of RRCTs relate to the ability to address some of the concerns of the conventional RCTs, including the inadequate representativeness of trial populations [17]. Embedding trials in clinical registries provides increased opportunity to systematically offer trial participation to "real-world patients" rather than opportunistically identifying potential trial participants. Studies comparing baseline characteristics of RCT trial populations with registry samples have identified lower risk profiles, with frequent exclusion of elderly patients and those with co-morbidities [18]. Trial designs that recruit from real-world populations are likely to improve the external validity of the trial findings, providing physicians with appropriate evidence on which to base clinical decisions [19]. However, the population coverage and representativeness of the clinical registry used for a RRCT also needs to be considered when generalising from such trials.

Randomisation and Treatment Exposure Assessment in RRCTs

Randomisation can be readily achieved with web-based randomisation modules that can be linked to registry databases. Non-commercial, smartphone-accessible applications can enable rapid, accurate randomisation at the bedside making them highly suitable for adoption into registry-based trials [20]. Assuring adequate treatment exposure in RRCTs remains a similar challenge to conventional RCTs. Depending on the trial design, individuals or groups of patient's treatment allocation will be determined at the point of randomisation. In procedural

registries, where the actual procedure to be undertaken varies, routine registry data collection should identify the procedural activity and highlight protocol deviations. In disease and health service registries, drug allocation, treatment compliance and persistence monitoring are required to ensure adequate treatment exposure – similar to conventional RCTs. The efficiency gain in RRCTs relies on the information being collected as part of routine registry follow-up data collection, but does not exclude other data being collected, such as data relevant to treatment compliance.

Outcome Information and Endpoint validation

Endpoint validation is an important consideration, particularly where data are collected from different institutions: there must be consistency in data definition and data collection. A fundamental difference from clinical trials endpoints, which are chosen or designed to meet the needs of the intervention, registry-based endpoints may have been designed for vastly different purposes. The accuracy of clinical endpoint determination using registry data as compared to active source data collection, follow-up, and clinical adjudication is currently unknown. Some registry outcomes may be linked or aligned to ICD-10 codes. Internationally, Australia is unique in its adoption of ICD-10 coding for hospital reimbursement, and coding standards differ between states and territories. There is some evidence to suggest poor agreement between ICD-10 coding and clinical audit [21]. Adjudication of events within registry trials may therefore be necessary to ensure the quality of risk factor and outcomes data [7]. One approach is having a *Clinical Event Adjudication Committee* adjudicate a subset of randomly identified events. Linking data to other datasets (e.g. National Death Index) can also be used for validation, where such datasets are available.

What designs are available for RRCT?

RRCTs are particularly useful when assessing real-world implementation of interventions [7]. RRCTs can take a number of designs, including individual level randomised controlled trials, parallel group trials, platform or adaptive trials, cluster randomised trials (CRT), and stepped-

wedge cluster randomised trials (SW-CRT). Adaptive randomisation may occur within pre-specified subgroups. While randomisation at the individual level has been more commonly used in RRCTs to date [7], cluster randomisation is increasingly reported [7 22], and has several distinct advantages, including overcoming administrative barriers and reducing costs [22].

Several types of *cluster randomised trial* design may be used in RRCTs (see Figure 1). In each of these study types, clusters (e.g., hospitals, GP practices etc) are randomised rather than individual patients. Similar to other trial designs, in cluster randomised trials the clustering effects need to be considered. For example, we might expect that mortality risk would vary across intensive care units, but patients within the same intensive care unit are likely to have similar mortality risk. This is called 'within-cluster correlation', and as such, the information per patient is not independent. There is some loss of statistical information in cluster randomised trials which leads to increased sample sizes requirements, however, this is typically offset by the ease of identifying and recruiting patients.

Parallel cluster RCT are similar to individual patient RCTs, except that randomisation occurs at the level of the cluster rather than the patient. Each cluster is randomly allocated to an intervention and remains with that intervention for the duration of the trial. In these studies, the information per patient is not independent leading to a loss of information, counterbalanced by greater number of recruited patients. However, these studies are relatively simple to analyse and interpret.

In the *cluster crossover* design, clusters switch between interventions, and the effect of the intervention is estimated by comparisons within each cluster, removing the between-cluster variability. Thus, this design requires fewer clusters and fewer patients than the parallel design. However, in this design, within-period correlations and between-period correlations must both be considered, and the design necessitates that the between-period correlation is smaller than the within-period correlation, because their relative size determines the value of

the crossover. Not all individually randomised trials are suitable for conduct as a cluster crossover trial: treatments must be able to be implemented and withdrawn easily; carryover effects must be avoided; and all patients must be recruited from the registry.

Stepped-wedge cluster randomised trial designs are beneficial where there is a risk of individuals in the control arm being accidentally exposed to the intervention. They are particularly useful in the general practice setting, or when implementing guidelines, training or system changes. In a SW-CRT design, all clusters start in the control phase and randomisation determines the order in which the intervention is implemented. Clusters (or groups of clusters) are randomly assigned to a time point when they cross over from control to intervention phase (step/sequence/arm). The SW-CRT can be designed with data collected cross-sectionally from different samples of individuals at each timepoint. Alternatively, data may be collected from a closed cohort, where individuals are followed longitudinally over the entire period of the trial and repeated measures are taken on the same individual at each time point. No new individuals join after the study starts. In an open cohort, data are collected on the same individuals over time, but new individuals can join over the study duration. At the end of the trial all clusters are in the intervention phase. Clusters are followed-up longitudinally, with outcomes/endpoints usually measured at discrete time points on individuals.

In SW-CRT, the sample size calculations need to allow for the effects of randomising clusters instead of individuals, those attending the same institution are more likely to have similar results than those attending elsewhere. The positive correlation of individuals within the same cluster is quantified with the intra-cluster correlation (ICC). The ICC measures the proportion of the total variance attributable to the variance between clusters. The extra variability between clusters in CRT has implications for the sample size and analysis. SW-CRT assume the full effect of the intervention occurs at the same time interval when intervention is introduced. A delay of intervention effect reduces the study power given a

fixed number of cluster and participants. One approach to ensure that the required power is maintained is to add additional measurement periods.

Advantages and disadvantages of various RRCT designs are summarised in Table 4.

Extracting data from the electronic medical record to develop virtual registries

Electronic data capture and integration with the electronic medical record has the potential to improve data validity and the efficiency of data collection, both of critical importance for clinical trials [12]. Utilising routinely collected medical record data in an automated fashion for determining clinical trial eligibility according to inclusion and exclusion criteria could greatly facilitate trial recruitment. Using routinely collected electronic medical record data, entered by clinicians at the time of diagnosis and treatment, for automated outcome ascertainment may also reduce time and costs and efficiency in conducting trials. There has been interest in using medical records as a data source for performing clinical analytics as early as the 1960s [23]. Medical records contain a tremendous accumulation of data, and it was hoped that electronic data processing systems would allow for organised, chronological records of patient information that could be used to facilitate research and hospital reporting [23]. It has recently been suggested that linkage of electronic medical records can be successfully used to provide near real-time clinical audit with feedback to clinicians, and provide a framework for clinical decision support [24].

Overcoming the technical and legal issues associated with data linkage to the electronic medical record can be a barrier [12]; not the least that there are a large number of different electronic medical record (eMR) platforms currently in use. . Currently the majority of data existing in the electronic medical record is free text, requiring careful mapping and validation. Text mining and natural language processing approaches to electronic medical records may assist in accurate patient identification and data collection. The adoption of universal

definitions of clinical events coded into EMRs would be an important development in the use of these systems for RRCTs. This requires a collaborative approach including the eMR developer, data architect, data scientist, data analyst and clinicians. There are already successful examples of combining data from registries with the electronic health record [25]. The development of privacy preserved record linkage capabilities will further facilitate the extended linking of administrative and clinical trial datasets for monitoring of health outcomes [26]. This approach to data linkage has been highlighted as a priority area for clinical quality registries in order to facilitate their use for research purposes [2].

Embedding trials into registries

In order to embed trials into registries, triallists must reach a compromise between a 'broad but shallow' data collection methodology typical of many registries, and the 'narrow but deep' approach for trial-related data collection, often needing to accept simpler accountability than seen in more traditional RCT approaches. In countries with well-established national registries, with standardised endpoints and little missing data, RRCTs offer a viable alternative to RCTs for generating high-quality clinical evidence [7]. By addressing issues of endpoint validity and adjudication, and decreasing the proportion of missing data, smaller disease or procedure focused registries might be able to improve the quality of their evidence, and in turn become a viable alternative platform than more costly RCTs [7]. For this reason it may be advantageous to initially embed RRCTs into registries that are already well established [7]. Internationally, registry data are becoming increasingly important in regulatory assessments, especially for post-marketing safety and effectiveness studies [27]. The key pillars when considering embedding a RRCT are outlined in Figure 2.

Best practice requires registries to be adequately resourced, so that data quality is maximised. Should the RRCT be a feasible option for a given registry and for a clinical questions, careful delineation of responsibilities regarding randomisation, missing data, handling of data queries, data quality, data extraction, and management of serious adverse event information

need to be considered. We suggest that the first two are the responsibility of the registry, the last is the responsibility of the trialist, and data queries could be attended to by either the registry or triallist. This requires adequate funding both of the registry itself and the RCT embedded within it. However, the benefits may far outweigh the cost. RRCTs allow for potential collaboration between clinical trial networks and clinical quality registries in related disciplines. The shared data management responsibilities between these potentially avoids data wastage for once-only use in more traditional clinical trials, and also improves the quality of data available within the registry. In some cases RRCTs may not the best approach, such as in earlier phase 2 or phase 3 clinical trials.

One of the key benefits of embedding clinical trials into registries is that following the trial's conclusion, the translation of evidence generated within that trial can then be assessed using the ongoing clinical registry. This addresses one of the key drawbacks of traditional randomised trials – there is no direct way to measure whether or not their findings have been implemented, and whether they translate to real-world practice.

Finally, there is also increasing interest in facilitating long-term follow-up post RCT using linked administrative and registry data [28]. A number of large scale clinical trials have utilised this method to report of longer term observational clinical outcomes following the shorter term observation of the clinical trials [29-31]. This strategy is valuable for mandatory reporting registries, such as cancer and death registries and provides valuable information in relation to long terms outcomes following a particular intervention or treatment. However, it has also proven valuable for trials of acute interventions and shorter term follow-up in COVID-19 treatment trials [32].

Conclusion

Registries offer a unique platform within which to conduct RCTs. With appropriate registry selection and clinical trial design, and advances in data linkage and data quality, RRCTs can play an important role in answering clinical questions in a pragmatic, cost-effective way.

Authors contributions

As per ICMJE criteria for authorship, all authors (DAD, ST, JRR, JS, SPM, SA, IAH, CT, AB, CH, LW, AB, BEB and CMR) made substantial contributions to the conception of this work, drafting the manuscript or revising it critically for important intellectual content, and approved the final version to be published. All authors (DAD, ST, JRR, JS, SPM, SA, IAH, CT, AB, CH, LW, AB, BEB and CMR) agree to be accountable for all aspects of the work in ensuring that questions raised relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding statement

This work was supported by an Australian Government Medical Research Future Fund grant through the 2017 Lifting Clinical Trials and Registries Capacity - Clinical Trials Networks Program.

Competing Interest

CMR is funded through a NHMRC Principal Research Fellowship (GHT1136372). CH is funded by a national Heart Foundation Fellowship and an NHMRC Investigator Grant. JR is funded by an Australian Government Research Training Program (RTP) Scholarship and a Monash University Graduate Excellence Scholarship.

References

1. Australian Commission on Safety and Quality in Health Care. National arrangements for clinical quality registries. Available from https://www.safetyandquality.gov.au/our-work/indicators-measurement-and-reporting/national-arrangements-clinical-quality-registries Accessed 2 December 2020. 2019 [

2. Australian Government - Department of Health. National Clinical Quality Registry and Virtual Registry Strategy 2020-2030, 2021.

3. James S, Fröbert O, Lagerqvist B. Cardiovascular registries: a novel platform for randomised clinical trials. *Heart* 2012;98(18):1329. doi: 10.1136/heartjnl-2012-301727

4. Everett CC, Fox KAA, Reynolds C, et al. Evaluation of the impact of the GRACE risk score on the management and outcome of patients hospitalised with non-ST elevation acute coronary syndrome in the UK: protocol of the UKGRIS cluster-randomised registry-based trial. *BMJ Open* 2019;9(9):e032165. doi: 10.1136/bmjopen-2019-032165

5. Menon BK, Buck BH, Singh N, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *The Lancet* 2022;400(10347):161-69. doi: https://doi.org/10.1016/S0140-6736(22)01054-6

6. Rasmussen JF, Siersma V, Pedersen JH, et al. Healthcare costs in the Danish randomised controlled lung cancer CT-screening trial: A registry study. *Lung Cancer* 2014;83(3):347-55. doi: https://doi.org/10.1016/j.lungcan.2013.12.005

7. Karanatsios B, Prang K-H, Verbunt E, et al. Defining key design elements of registry-based randomised controlled trials: a scoping review. *Trials* 2020;21(1):1-22.

8. Fröbert O, Lagerqvist B, Gudnason T, et al. Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and

angioplasty registry (SCAAR) platform. Study design and rationale. *American heart journal* 2010;160(6):1042-48.

9. Lauer MS, D'Agostino Sr RB. The randomized registry trial--the next disruptive technology in clinical research? *The New England journal of medicine* 2013;369(17):1579.

10. Gitt AK, Bueno H, Danchin N, et al. The role of cardiac registries in evidence-based medicine. *Eur Heart J* 2010;31(5):525-9. doi: 10.1093/eurheartj/ehp596 [published Online First: 2010/01/23]

11. Hoque DME, Kumari V, Hoque M, et al. Impact of clinical registries on quality of patient care and clinical outcomes: A systematic review. *PLoS One* 2017;12(9):e0183667. doi: 10.1371/journal.pone.0183667 [published Online First: 2017/09/09]

12. Sparring V, Granström E, Andreen Sachs M, et al. One size fits none – a qualitative study investigating nine national quality registries' conditions for use in quality improvement, research and interaction with patients. *BMC Health Services Research* 2018;18(1) doi: 10.1186/s12913-018-3621-9

13. Australian Commission on Safety and Quality in Health Care. Economic evaluation of clinical quality registries: Final report. Sydney: ACSQHC, 2016.

14. Lasch F, Weber K, Koch A. Commentary: On the levels of patient selection in registry-based randomized controlled trials. *Trials* 2019;20(1):100. doi: 10.1186/s13063-019-3214-x [published Online First: 2019/02/06]

15. James S, Rao SV, Granger CB. Registry-based randomized clinical trials--a new clinical trial paradigm. *Nat Rev Cardiol* 2015;12(5):312-6. doi: 10.1038/nrcardio.2015.33 [published Online First: 2015/03/18]

16. Yndigegn T, Hofmann R, Jernberg T, et al. Registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era. *Heart* 2018;104(19):1562-67. doi: 10.1136/heartjnl-2017-312322 [published Online First: 2018/04/19]

17. Antman EM, Harrington RA. Transforming clinical trials in cardiovascular disease: mission critical for health and economic well-being. *Jama* 2012;308(17):1743-44.

18. Kennedy-Martin T, Curtis S, Faries D, et al. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* 2015;16(1):495. doi: 10.1186/s13063-015-1023-4

19. Collins MG, Fahim MA, Pascoe EM, et al. Baseline Characteristics and Representativeness of Participants in the BEST-Fluids Trial: A Randomized Trial of Balanced Crystalloid Solution Versus Saline in Deceased Donor Kidney Transplantation. *Transplant Direct* 2022;8(12):e1399. doi: 10.1097/txd.0000000000001399 [published Online First: 20221104]

20. Badurdeen S, Hodgson KA, Santomartino GA, et al. Rapid centralised randomisation in emergency setting trials using a smartphone. *European Journal of Pediatrics* 2022;181(8):3207-10. doi: 10.1007/s00431-022-04475-y

21. Reilly JR, Shulman MA, Gilbert AM, et al. Towards a national perioperative clinical quality registry: the diagnostic accuracy of administrative data in identifying major

postoperative complications. *Anaesth Intensive Care* 2020:310057X20905606. doi: 10.1177/0310057X20905606 [published Online First: 2020/04/30]

22. Moberg J, Kramer M. A brief history of the cluster randomised trial design. *Journal of the Royal Society of Medicine* 2015;108(5):192-8. doi: 10.1177/0141076815582303 [published Online First: 2015/05/30]

23. Baird HW, Garfunkel JM. Electronic Data Processing of Medical Records. *New England Journal of Medicine* 1965;272(23):1211-15. doi: 10.1056/nejm196506102722306

24. Saavedra A, Morris RW, Tam CS, et al. Validation of acute myocardial infarction (AMI) in electronic medical records: the SPEED-EXTRACT study. 2020 doi: 10.1101/2020.12.08.20245720

25. Kibbelaar RE, Oortgiesen BE, van der Wal-Oost AM, et al. Bridging the gap between the randomised clinical trial world and the real world by combination of population-based registry and electronic health record data: A case study in haemato-oncology. *European Journal of Cancer* 2017;86:178-85. doi: https://doi.org/10.1016/j.ejca.2017.09.007

26. Brown AP, Randall SM, Ferrante AM, et al. Estimating parameters for probabilistic linkage of privacy-preserved datasets. *BMC Med Res Methodol* 2017;17(1):95. doi: 10.1186/s12874-017-0370-0 [published Online First: 2017/07/12]

27. McGettigan P, Alonso Olmo C, Plueschke K, et al. Patient Registries: An Underused Resource for Medicines Evaluation. *Drug Safety* 2019;42(11):1343-51. doi: 10.1007/s40264-019-00848-9

28. Fitzpatrick T, Perrier L, Tricco AC, et al. Protocol for a scoping review of post-trial extensions of randomised controlled trials using individually linked administrative and registry data. *BMJ open* 2017;7(2):e013770. doi: 10.1136/bmjopen-2016-013770 [published Online First: 2017/02/19]

29. Lehtinen M, Lagheden C, Luostarinen T, et al. Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia end-point—registry-based follow-up of three cohorts from randomized trials. *BMJ open* 2017;7(8):e015867.

30. Gallagher M, Jardine M, Perkovic V, et al. Cyclosporine withdrawal improves long-term graft survival in renal transplantation. *Transplantation* 2009;87(12):1877-83. doi: 10.1097/TP.0b013e3181a76823

31. Clayton PA, McDonald SP, Chapman JR, et al. Mycophenolate versus azathioprine for kidney transplantation: a 15-year follow-up of a randomized trial. *Transplantation* 2012;94(2):152-8. doi: 10.1097/TP.0b013e31825475a3

32. Recovery Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet* 2022;400(10349):359-68. doi: 10.1016/s0140-6736(22)01109-6

33. Li G, Sajobi TT, Menon BK, et al. Registry-based randomized controlled trials- what are the advantages, challenges, and areas for future research? *J Clin Epidemiol* 2016;80:16-24. doi: 10.1016/j.jclinepi.2016.08.003 [published Online First: 2016/10/22]

34. Donner A, Klar N. Pitfalls of and controversies in cluster randomization trials. *Am J Public Health* 2004;94(3):416-22. doi: 10.2105/ajph.94.3.416 [published Online First: 2004/03/05]

35. Peptic Investigators for the Australian New Zealand Intensive Care Society Clinical Trials Group AHSCCSCN, The Irish Critical Care Trials Group, Young PJ, et al. Effect of Stress Ulcer Prophylaxis With Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation: The PEPTIC Randomized Clinical Trial. *Jama* 2020;323(7):616-26. doi: 10.1001/jama.2019.22190 [published Online First: 2020/01/18]

36. Li AH, Garg AX, Prakash V, et al. Promoting deceased organ and tissue donation registration in family physician waiting rooms (RegisterNow-1 trial): study protocol for a pragmatic, stepped-wedge, cluster randomized controlled registry. *Trials* 2017;18(1):610. doi: 10.1186/s13063-017-2333-5 [published Online First: 2017/12/23]

Tables

Table 1: Glossary of Terms

Term	Definition
Clinical quality registry	Clinical quality registries use clinical data to identify benchmarks and variation in clinical outcomes and feed-back essential risk-adjusted clinical information, to clinicians, patients, consumers, health service administrators and government to inform clinical practice and health service decision making [1].
Cluster	A cluster is a group of patients. It may be a hospital, a GP practice, a group of patients treated by an individual clinician etc.
Cluster crossover trial	A cross-over trial where the unit of randomisation is a cluster.
Cluster randomised trial	A randomised trial where the unit of randomisation is a cluster.
Cross over trial (individual patient randomisation)	A cross-over trial where the unit of randomisation is the patient. A crossover trial involves patients being treated sequentially with two (or more) treatments of interest.
Parallel arm trial (individual patient randomisation)	A trial where the unit of randomisation is the patient. Patients are randomised to receive one treatment of interest.

Parallel cluster randomised controlled trial	A trial where clusters are randomised to receive one treatment of interest.
Registry randomised clinical trial	A randomised clinical trial that is embedded into a registry.
Stepped-wedge cluster randomised trial	A trial where clusters are randomised to receive control then intervention/treatment in a stepped fashion. That is, the timing of the switch to intervention/treatment is randomised (see also Figure 1).

Table 2: Six pillars underpinning clinical quality registries in Australia

1. Patient-centred health care

   Registries can help to identify variability in patient reported outcomes; support clinicians to tailor care to individual needs and preferences; support equity of health care. Datasets should therefore contain a combination of clinician and patient-derived data; and should have clinician oversight.

2. Improved clinical practice care and patient outcomes

   Datasets should have mechanisms for 'benchmarking' where clinicians, health service and other stakeholders are provided with feedback on their care provision 'benchmarking'.

3. Quality, efficiency and cost effectiveness

   Improve the quality and efficiency of data collection. Improve governance and allow data sharing: 'collect one, use multiple times principle'. This requires data linkage, where possible, to reduce burden. Data collection should be standardised, and follow national health data and terminology standards and definitions.

4. Financial sustainability

   Sufficient, sustainable funding is required. The funding model may include partnerships with multiple beneficiaries. In this context, funding via clinical trials might also be appropriate.

5. Transparency and access

   Timely provision of tailored information to patients, hospitals, jurisdictions,

governments, funders, private health insurers, researchers and other stakeholders, while upholding patient privacy.

6. Data linkage, integration and interoperability

By improving linkage, a more comprehensive, longitudinal picture of patient treatment and outcomes than is currently available will be possible. This will also allow for increased analytical power and provide more cost effective clinical trials and more comprehensive post-market surveillance of devices and medicines.

Table 3: Advantages and disadvantages of RRCT

Potential Advantages	Potential Disadvantages
• In many cases, reduced time for data collection compared to RCT [11] • Reduced database costs compared to RCT as embedded into existing infrastructure • reduced data collection costs as data extracted for the registry is leveraged for the clinical trial • Include patients identified and recruited from within a registry [33] • All interventions and outcomes are captured in the registry [33] • Less selected patient population compared to traditional RCT [15] hence improved external validity compared to traditional RCT	• Limited endpoint selection • Endpoints might not be well defined [15] • Missing data • Variable data quality [15] • Data entry may occur sometime after original clinical data collection

Table 4: Advantages and disadvantages of various registry randomised controlled trial designs

Design	Advantages	Disadvantages
Parallel group cluster RCT	• Easy to analyse and interpret • Randomisation removes potential confounding [15] • Increased administrative efficiency [34] • Easy to recruit patients [7] • Cost effective [7] • Potential for large number of events allows for identification of rare events [15]	• Increased risk of bias compared to individual patient RCT • Limited possibility for collection of detailed safety reporting [15] • Less efficient than individual level RCT
Cluster crossover RCT e.g PEPTIC [35] (see Case Study 3)	• Randomisation removes potential confounding [15] • Randomised clusters serve as their own controls • Avoids potential contamination of control with intervention [34] • Includes all patients within a cluster	• Increased risk of bias compared to individual patient RCT • Increased burden on participants • Not all studies can be implemented using these methods: treatments must be able to be implemented and withdrawn easily

	• Assumes consent of patient (or recruitment often occurs under a waiver of consent) • Easy to recruit patients [7] • Cost effective [7] • Potential for large number of events allows for identification of rare events [15]	• Risk of carry over effects • Limited possibility for collection of detailed safety reporting [15] • Take longer to complete than a parallel group cluster RCT • Ethics committees may not be supportive of waiver of consent
Cluster stepped-wedge e.g. RegisterNow-1 [36] (See Case Study 4)	• Randomisation removes potential confounding [15] • Avoids potential contamination of control with intervention [34] • Easy to recruit patients [7] • Cost effective [7] • Potential for large number of events allows for identification of rare events [15]	• Takes longer to complete • Increased burden on participants • Increased risk of bias compared to individual patient RCT • No consensus for best approach to analysis • Limited possibility for collection of detailed safety reporting [15]

Figures

Figure 1: Possible designs for registry randomised trials

Figure 2: Key pillars when considering embedding a RRCT [27]

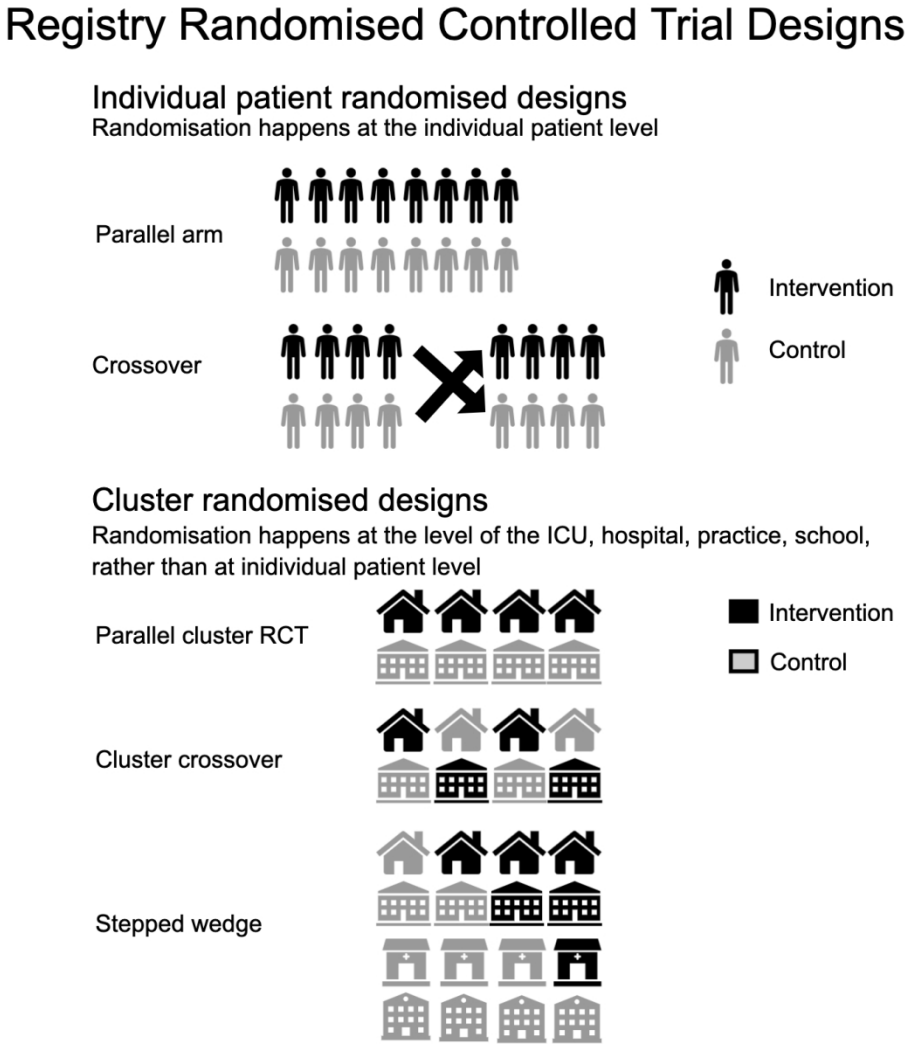

Figure 1: Possible designs for registry randomised trials

127x134mm (300 x 300 DPI)

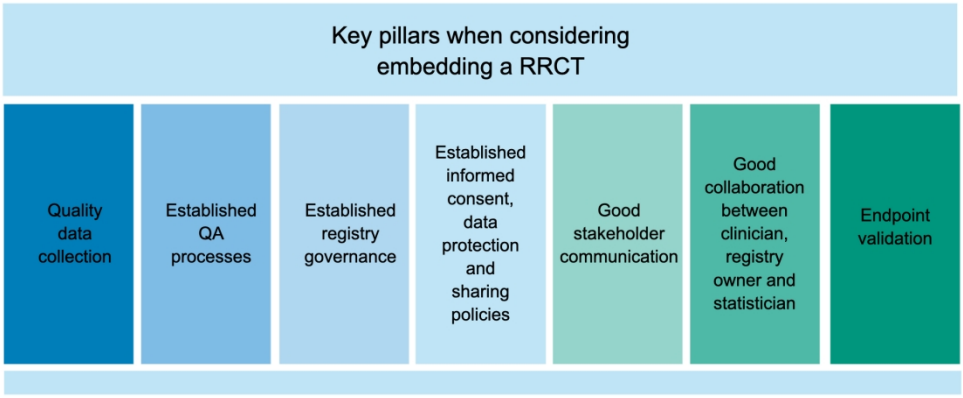

Figure 2: Key pillars when considering embedding a RRCT

172x71mm (300 x 300 DPI)